REMARKS

Claims 1-5, 7-13, 19-23, 25 and 26 presently appear in this case. No claims have been allowed. The official action of February 27, 2001, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for stimulating systemic host defense mechanisms by administering a therapeutically effective amount of an interferon via oromucosal contact. The amount is from 21.4 IU/kg/day to about 2.9×10^4 IU/kg/day. The oromucosal administration is in a manner which does not involve direct action of the interferon on virally infected cells. Preferably, the condition is other than a rhinovirus.

The interview among Examiners Andres and Eyler, Dr. Michael Tovey, who is the present inventor, and the undersigned attorney, conducted on June 19, 2001, is hereby gratefully acknowledged. In this interview, rebuttal evidence was discussed in an attempt to rebut the examiner's *prima facie* case of obviousness. It was argued that such evidence establishes that no *prima facie* case of obviousness has been established as there would have been no reasonable expectation by those of ordinary skill in the art that using twice as much interferon as the maximum disclosed by the primary reference would be effective. It was further argued that unexpected

results rebut any *prima facie* case of obviousness. While no specific agreement was reached, the examiners agreed to carefully consider applicant's submission of any new evidence.

Claims 1-5, 7-13, 19-23 and 25 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Cummins ('382) or Cummins ('456) in view of either Samo (1984) or Iida (1989). The examiner states that in each patent, Cummins teaches the use of interferons contacting the oral mucosa to treat neoplastic disease, viral disease and bacterial infection, but in each patent, Cummins teaches a maximum dose of 5 IU/lb/day or 11 IU/kg/day, whereas the instant claims encompass a range of 21.4 IU/kg/day to about 2.9×10^4 IU/kg/day. The examiner states that Samo teaches a range of $0.7\text{-}2.4 \times 10^6$ units and Iida teaches a range of $10\text{-}10^3$ units per mouse administered on one day intranasally, which is about 30-3000 IU/kg, assuming 0.1 IU per unit. The examiner notes that neither Samo nor Iida teaches treatment as both are drawn to prophylaxis. The examiner states that as Cummins discloses a broad range of more than two orders of magnitude for oromucosal doses effective for treatment of viral infection, and Samo and Iida teach that much higher doses are not toxic, one of ordinary skill in the art would reasonably expect that doses higher than those taught by Cummins would be effective in treatment of viral infection, with the expectation of

achieving a result at least as good as that achieved by Cummins. The examiner states that the lowest dose taught by applicant, which is about twice the maximum taught by Cummins, "would not seem to be significantly different from that taught by Cummins". This rejection is respectfully traversed.

As the examiner notes, Samo and Iida are directed only to prophylactic uses. They are not directed to the same utility to which either of the Cummins patents are directed. Therefore, the fact that they teach administering larger amounts of interferon would create no expectation as to what would happen if such large amounts were administered for the purpose of Cummins. Furthermore, Samo does not define how to determine the strength of the "units" that it refers to. It is inappropriate to refer to the concordance of Cummins (0.1 IU/unit) as the activity of interferon in a unit will vary from laboratory to laboratory unless actually compared to the international reference sample, which would then allow a concordance to international units. Therefore, it is inappropriate for the examiner to assume that the activity of a unit in the laboratory of Cummins would necessarily be the same as the activity of a unit in the laboratory of either Samo or Iida. Therefore, one really has no idea how much interferon is being used by Samo and Iida.

In view of the differences in utility between the Cummins patents on the one hand and Samo and Iida on the other, it is apparent that the examiner is relying on the secondary references only for a showing that the use of larger amounts would not be expected to be toxic. Accordingly, for the sake of the present argument only, it will be assumed that these references do disclose that those of ordinary skill in the art would not expect the amounts of interferon administered in accordance with the present invention to have toxic effects. Nevertheless, this knowledge, in combination with the disclosure of Cummins, would not create a *prima facie* case that those of ordinary skill in the art would have been motivated to use twice as much as the maximum disclosed by Cummins and to expect that amount to be at least as effective as the amounts specifically disclosed in Cummins.

The fact cannot be ignored that in both of the Cummins patents both a specific minimum amount of interferon and a specific maximum amount of interferon was specified. Even though the range between the minimum and the maximum spans more than 2.5 orders of magnitude, those of ordinary skill in the art would expect that there was some reason why a patent applicant would so limit his disclosure. One would not expect such an explicit maximum amount if it would be expected that amounts of interferon outside the specified range would

be effective, particularly in view of the fact that references, such as Samo, which was published prior to the effective filing date of Cummins, would teach those of ordinary skill in the art that amounts greater than the maximum of Cummins would not be toxic. When a patent applicant voluntarily limits his disclosure as filed to a maximum and a minimum in order to have the therapeutic effect, particularly when it would not be expected that larger amounts would be toxic, those of ordinary skill in the art would expect that there was a bell-shaped dose response curve such that amounts greater than the maximum and lower than the minimum would be expected to be substantially ineffective, regardless of how many orders of magnitude are in between. The minimum amount specified by the present claims is twice as much as the maximum taught to be effective by Cummins.[1] Thus, the examiner has not established a *prima facie* case that those of ordinary skill in the art would have been motivated to use at least twice as much as the maximum of Cummins and that such amounts would be effective for the purpose of Cummins. In this regard, the examiner's attention is drawn to *In re Steminski*, 170 USPQ 343, 347 (CCPA, 1971), where it states:

[1] It is not understood why the examiner refers to the difference between the minimum of the present claims and the maximum of Cummins in "orders of magnitude". One would have no reason to expect dose response to follow a logarithmic scale. On a normal scale, "double" is always significant.

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> [W]hat on this record - other than abstract, theoretical or academic considerations - would lead one of ordinary skill to change the structure of the reference compounds to obtain the claimed compounds? Certainly no practical considerations which promote the progress of useful arts or are of use to society are manifest. How can there be obviousness of structure, or particularly of the subject matter as a whole, when no apparent purpose or result is to be achieved, no reason or motivation to be satisfied, upon modifying the reference compounds' structure? Where the prior art reference neither discloses nor suggests a utility for certain described compounds, why should it be said that a reference makes obvious to one of ordinary skill in the art an isomer, homolog or analog or related structure, when that mythical, but intensely practical, person knows of no "practical" reason to make the reference compounds, much less any structurally related compounds? In short, of what significance is it to a determination of obviousness that it is reasonable to assume or expect the compounds of the prior art and of the claims to possess similarities in significant properties or uses, if in fact no one prior to appellant's entry into the field knew what any of those properties or uses are?

That intensely practical man of ordinary skill in the art would have no motivation whatsoever to use any amount greater than the maximum amount taught to be effective by Cummins. Samo and Iida create no expectation of <u>therapeutic</u> effectiveness of larger amounts than the maximum disclosed by Cummins for the therapeutic treatment taught by Cummins. Cummins does not teach that such larger amounts would be effective, and there would be no motivation whatsoever to use

larger amounts than the maximum disclosed by Cummins as there would be no reason or necessity for one to do so, particularly in view of the extreme expense of interferon (see Schofield et al, attached hereto, discussed *infra*).

In support of this argument, the examiner's attention is invited to the attached declaration of Dr. Michael Tovey and the attachments thereto. In that declaration, in the paragraph bridging pages 2 and 3, and the following paragraph, Dr. Tovey notes that conventional wisdom would hold that indirect immunological stimulation of a substance that is not absorbed by the organism in appreciable quantities would not be dose responsive. He points out previous reports that interferon stimulation of immune-mediated effects, which is effective in low doses, is inhibitory at higher doses. These include such immune-mediated effects as NK cell cytotoxicity, antibody production and major histocompatibility antigen expression. Papers or abstracts supporting these conclusions are attached to the declaration. Also supporting this argument and attached hereto is an abstract of Schofield et al, "Low doses of interferon-α are as effective as higher doses in inducing remissions and prolonging survival in chronic myeloid leukemia", Ann Intern Med 121:736-744 (1994).

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On the other hand, the present inventor has surprisingly found that the antiviral activity of oromucosal interferon therapy is dose responsive. The more one uses, the better the effect. The declaration attaches Dr. Tovey's paper in J Interferon Cytokine Res which establishes this dose responsiveness. This dose responsiveness was surprising to Dr. Tovey, the inventor of the present application. Those of ordinary skill in the art at the time the present invention was made would have no reasonable expectation that the use of an amount of interferon twice that of the maximum specified by Cummins, or higher, would be effective; indeed, they might have expected it to be ineffective. Rebutting the examiner's *prima facie* case of obviousness, the evidence of record establishes that the more interferon is used, the more effective is the treatment when administered in the manner of the present invention.

Accordingly, the evidence of record establishes that those of ordinary skill in the art reading Cummins would expect that, when Cummins sets a maximum in his patent specification, he intended that as a maximum and, in view of other publications of record at the time of the present invention, one would expect that this is a situation of immunostimulation where higher amounts are not better than low

amounts. Thus, no *prima facie* case of obviousness has been established by the examiner.

Furthermore, regardless of whether a valid *prima facie* case of obviousness has been established, the evidence of record rebuts this *prima facie* case of obviousness because the experimental results unexpectedly show a classic dose response curve where the more interferon administered oromucosally, the better the effect. This would not have been expected by one of ordinary skill in the art in view of the maximum set by Cummins and the other evidence of record that less is expected to be better than more when dealing with indirect immunological stimulation by a substance that it is not absorbed by the organism in appreciable quantities.

Furthermore, new claim 26 has now been added in Jepson format in accordance with a suggestion of Examiner Eyler. The improvement obtained by higher doses than the maximum taught by Cummins is unexpected. This improvement is more clearly set forth in a Jepson-style claim. If the examiner believes that this format of claim would be more likely to overcome the rejection of record, then applicant would be willing to delete claim 1 in favor of the Jepson claim and amend all of the dependent claims so as to depend from the Jepson claim.

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Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

Claims 1, 3-5, 7-13, 22, 23 and 25 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The examiner states that the negative limitation that the administration does not involve direct action is a limitation on the mechanism with no corresponding method step to achieve that outcome. This rejection is respectfully traversed.

Claim 1 has now been amended to specify that the oromucosal administration is "such that it does not involve direct action of the interferon on virally infected cells". This is a direct limitation on the method step as the present claim does not read on intranasal administration of interferon onto cells of the nasal mucosa which are already infected with a rhinovirus. Since it is now more clear that the intent of the claim is to exclude any manner of administration which involves direct action of the interferon on virally-infected cells, it can be seen that there is a corresponding limitation to the method step which achieves the mechanism outcome referred to by the examiner. Reconsideration and withdrawal of this rejection are, therefore, also respectfully urged.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current

amendment. The attached page is captioned "Version with markings to show changes made".

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are, therefore, earnestly solicited.

Respectfully submitted,

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